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## Burden and Timeline of Infectious Diseases in the First Year After Solid Organ Transplantation in the Swiss Transplant Cohort Study

Swiss Transplant Cohort Study ; van Delden, Christian ; Stampf, Susanne ; Hirsch, Hans H ; Manuel, Oriol ; Meylan, Pascal ; Cusini, Alexia ; Hirzel, Cédric ; Khanna, Nina ; Weisser, Maja ; Garzoni, Christian ; Boggian, Katja ; Berger, Christoph ; Nadal, David ; Koller, Michael ; Saccilotto, Ramon ; Mueller, Nicolas J

**Abstract:** **BACKGROUND** The burden and timeline of posttransplant infections are not comprehensively documented in the current era of immunosuppression and prophylaxis. **METHODS** In this prospective study nested within the Swiss Transplant Cohort Study (STCS), all clinically relevant infections were identified by transplant-infectious diseases physicians in persons receiving solid organ transplant (SOT) between May 2008 and December 2014 with 12 months of follow-up. **RESULTS** Among 3541 SOT recipients, 2761 (1612 kidney, 577 liver, 286 lung, 213 heart, and 73 kidney-pancreas) had 12 months of follow-up; 1520 patients (55%) suffered 3520 infections during the first year posttransplantation. Burden and timelines of clinically relevant infections differed between transplantations. Bacteria were responsible for 2202 infections (63%) prevailing throughout the year, with a predominance of Enterobacteriaceae (54%) as urinary pathogens in heart, lung, and kidney transplant recipients, and as digestive tract pathogens in liver transplant recipients. Enterococcus spp (20%) occurred as urinary tract pathogens in kidney transplant recipients and as digestive tract pathogens in liver transplant recipients, and Pseudomonas aeruginosa (9%) in lung transplant recipients. Among 1039 viral infections, herpesviruses predominated (51%) in kidney, liver, and heart transplant recipients. Among 263 fungal infections, Candida spp (60%) prevailed as digestive tract pathogens in liver transplant recipients. Opportunistic pathogens, including Aspergillus fumigatus (1.4%) and cytomegalovirus (6%), were rare, scattering over 12 months across all SOT recipients. **CONCLUSIONS** In the current era of immunosuppression and prophylaxis, SOT recipients experience a high burden of infections throughout the first year posttransplantation, with rare opportunistic pathogens and a predominance of bacteria.

DOI: <https://doi.org/10.1093/cid/ciz1113>

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ZORA URL: <https://doi.org/10.5167/uzh-180991>

Journal Article

Published Version



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Originally published at:

Swiss Transplant Cohort Study; van Delden, Christian; Stampf, Susanne; Hirsch, Hans H; Manuel, Oriol; Meylan, Pascal; Cusini, Alexia; Hirzel, Cédric; Khanna, Nina; Weisser, Maja; Garzoni, Christian; Boggian, Katja; Berger, Christoph; Nadal, David; Koller, Michael; Saccilotto, Ramon; Mueller, Nicolas J (2020). Burden and Timeline of Infectious Diseases in the First Year After Solid Organ Transplantation in the Swiss Transplant Cohort Study. *Clinical Infectious Diseases*, 71(7):e159-e169.  
DOI: <https://doi.org/10.1093/cid/ciz1113>

# Burden and Timeline of Infectious Diseases in the First Year After Solid Organ Transplantation in the Swiss Transplant Cohort Study

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**Background.** The burden and timeline of posttransplant infections are not comprehensively documented in the current era of immunosuppression and prophylaxis.

**Methods.** In this prospective study nested within the Swiss Transplant Cohort Study (STCS), all clinically relevant infections were identified by transplant-infectious diseases physicians in persons receiving solid organ transplant (SOT) between May 2008 and December 2014 with  $\geq 12$  months of follow-up.

**Results.** Among 3541 SOT recipients, 2761 (1612 kidney, 577 liver, 286 lung, 213 heart, and 73 kidney-pancreas) had  $\geq 12$  months of follow-up; 1520 patients (55%) suffered 3520 infections during the first year posttransplantation. Burden and timelines of clinically relevant infections differed between transplantations. Bacteria were responsible for 2202 infections (63%) prevailing throughout the year, with a predominance of Enterobacteriaceae (54%) as urinary pathogens in heart, lung, and kidney transplant recipients, and as digestive tract pathogens in liver transplant recipients. *Enterococcus* spp (20%) occurred as urinary tract pathogens in kidney transplant recipients and as digestive tract pathogens in liver transplant recipients, and *Pseudomonas aeruginosa* (9%) in lung transplant recipients. Among 1039 viral infections, herpesviruses predominated (51%) in kidney, liver, and heart transplant recipients. Among 263 fungal infections, *Candida* spp (60%) prevailed as digestive tract pathogens in liver transplant recipients. Opportunistic pathogens, including *Aspergillus fumigatus* (1.4%) and cytomegalovirus (6%), were rare, scattering over 12 months across all SOT recipients.

**Conclusions.** In the current era of immunosuppression and prophylaxis, SOT recipients experience a high burden of infections throughout the first year posttransplantation, with rare opportunistic pathogens and a predominance of bacteria.

**Keywords.** infection; bacterial; fungal; viral; solid organ transplant.

Solid organ transplant (SOT) recipients require long-term immunosuppression and are at risk for life-threatening infections. Three periods of infections after transplantation have been distinguished: (1) a phase up to 1 month characterized

by nosocomial infections and donor-derived infections; (2) a phase of profound immunosuppression for up to 6 months associated with opportunistic infections; and (3) a phase of reduced immunosuppression with community-acquired and rare infectious agents [1–3].

The awareness of this temporal pattern has allowed tailoring of prophylactic strategies, diagnostic testing, and empiric therapies. Since the review of this concept in 1998, new potent immunosuppressive strategies have reduced the incidence of rejection, but at the same time altered recipients' susceptibility to infections. Concomitantly, the availability of efficient prophylaxis may have modified frequencies and temporal patterns of posttransplant infections [2, 4–6]. Knowledge of timing and relative frequencies of infections in the era of extended donor/recipient criteria, modern immunosuppression, routine use of prophylaxis, and active surveillance of viral replication is

Received 2 July 2019; editorial decision 5 November 2019; accepted 11 November 2019; published online January 9, 2020.

<sup>a</sup>Active members of the Swiss Transplant Cohort Study are listed in the Appendix.

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Clinical Infectious Diseases® 2019;XX(XX):1–11

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crucial for implementing prevention strategies to further reduce morbidity and mortality associated with posttransplant infections. Registries provide important data in this regard but are restricted by a limited number of selected infections, and lack both stringent patient follow-up and standardized definitions of infections. Only a few studies have prospectively and comprehensively recorded the incidence of specific infections and been able to estimate the relative burden and timeline patterns of certain pathogens [4, 5, 7].

Since May 2008, the Swiss Transplant Cohort Study (STCS) has enrolled 93% of all SOT recipients in Switzerland, and provides an ideal source to extract data on all aspects of transplantation including infections. Using prespecified rigorous definitions [8] and transplant center review, we analyzed comprehensive data on 3520 clinically relevant infections occurring in the first year after transplantation among 2761 SOT recipients in Switzerland.

## METHODS

### Characteristics of the STCS

The STCS prospectively enrolls all SOT recipients undergoing transplantation in Switzerland [8]. Designed as a patient-case system, the database captures both patient- and graft-specific data. Clinical and laboratory data are continuously collected and entered in the database at the time of transplantation, at 6 and 12 months, then yearly thereafter. The STCS Central Data Center performs regular data monitoring and in-depth data quality audits. In this process, all participating centers and all types of transplants are assessed by a thorough review process of randomly sampled patients. Ethics approval was obtained in all participating centers; all enrolled patients gave written informed consent. The study was approved by the Scientific Committee of the STCS, which granted permission to the investigators to use the data from the STCS.

### Patients

All adult recipients of lung, heart, liver, kidney, and kidney-pancreas grafts in Switzerland and enrolled in the STCS between 1 May 2008 and 31 December 2014 were included.

### Infections

All infections were identified by transplant-infectious disease (TID) physicians using electronic hospital records and referral documentation for both inpatients and outpatients in intervals ranging from twice a week to every 3 months, according to standardized definitions (Supplementary Data). The definitions were developed by the STCS infectious diseases working group, based on recommendations and guidelines proposed by the American Society of Transplantation Infectious Disease Community of Practice, and the European Conference on Infections in Leukemia [9, 10]. Particular care was taken to minimize the risk of miscoding colonization as “infection.” To

reduce the risk of intraobserver variability, randomly selected infections were evaluated by TID physicians during a quality review. In the present study, we considered as clinically relevant infections all proven bacterial, probable and proven fungal, and probable and proven viral infections, as well as viral syndromes (Supplementary Data).

Data on antimicrobial resistance were recorded by the STCS after August 2012. Multidrug resistance was defined according to international standards [11]. Infections in patients hospitalized for <24 hours were collected as outpatient infections.

### Immunosuppression and Prophylaxis

Immunosuppressive and preventive strategies were center specific and varied according to transplant (Supplementary Figures 1 and 2). All patients received peritransplant antibacterial prophylaxis for 48 hours, as well as oral nystatin prophylaxis for 14 days. To be recorded, prophylaxis required administration exceeding 48 hours and had to be targeted to prevent specific pathogens.

### Outcomes

The primary outcome was occurrence of clinically relevant infections within 12 months posttransplantation. Secondary outcomes included type of pathogen, time of infection, and distribution according to transplant type and infection sites.

### Statistical Analysis

Time of observation was calculated for each patient as time between transplantation and dropout, second transplant, or return to dialysis, death, or censoring date, whichever occurred first. Patients with graft failure leading to second transplantation were censored at the time of their second transplantation. Kidney transplant recipients returning to dialysis are censored from the STCS follow-up. Infection rates per person-time were calculated as the number of infections during the first year posttransplantation divided by person-time. Because the highest infection density was observed within 50 days posttransplantation, differences in cumulative incidences in infections were calculated at 49 days. Infection rates per 1000 transplant-days were calculated for each time span (during first month, >1–6 months, >6–12 months) in a negative binomial model.

## RESULTS

### Transplant Population and Incidence of Infections

Of 3541 lung, heart, liver, kidney, and kidney-pancreas transplant recipients since 1 May 2008 in Switzerland, 3304 patients (93%) consented to participate in the STCS (Supplementary Figure 3). Of these, 2761 patients had their first SOT between 1 May 2008 and 31 December 2014 and were included in this analysis. Patients received kidney ( $n = 1612$  [58%]), liver ( $n = 577$  [21%]), lung ( $n = 286$  [10%]), heart ( $n = 213$  [8%]),

and kidney-pancreas ( $n = 73$  [3%]) transplants (Table 1). During the first year posttransplantation, 80% (2210/2761) of these patients had 8562 infectious events recorded. A total of 3520 events in 1520 patients (55%) fulfilled the criteria for clinically relevant infections, further designated as infections. The infection rate per person-year was 1.3 (95% confidence interval [CI], 1.3–1.4). Of patients at risk, 27% (755/2761) had 989 infections (28% of all infections) during the first month (12.0 episodes per 1000 transplant-days), 33% (906/2714) had 1553 infections (44%) between 1 and 6 months (3.9 episodes per 1000 transplant-days), and 23% (609/2649) had

962 (28%) infections between 6 and 12 months following transplant (2.0 episodes per 1000 transplant-days) (Table 1; Supplementary Table 1). Infection rates were highest during the first month in heart (19.3 episodes per 1000 transplant-days) and lung (17.3 episodes per 1000 transplant-days) transplant recipients and remained highest in lung transplant recipients between 6 and 12 months (2.6 infections per 1000 transplant-days). Cumulative incidences varied by transplant type, with kidney transplant recipients having the lowest incidence of infections (12% and 27% at day 14 and 7 weeks, respectively) as compared to recipients of heart (hazard ratio

**Table 1. Characteristics of Patients, Infections, and Antimicrobial Prophylaxis**

Characteristic	Heart	Kidney	Kidney-Pancreas	Liver	Lung	Total
<b>Patient characteristics</b>						
Transplantations	213 (8)	1612 (58)	73 (3)	577 (21)	286 (10)	2761 (100)
Median age at transplantation, y (IQR)	52 (38–60)	54 (43–63)	44 (39–51)	54 (44–61)	54 (38–61)	54 (42–62)
Male sex	160 (75)	1034 (64)	39 (53)	382 (66)	143 (50)	1758 (64)
Any infectious event	167 (78)	1303 (81)	65 (89)	457 (79)	218 (76)	2210 (80)
Any clinically relevant infection	128 (60)	852 (53)	44 (60)	320 (56)	176 (62)	1520 (55)
Deaths (by infection)	32 (7)	41 (12)	1 (0)	57 (24)	30 (9)	161 (52)
<b>Infections</b>						
Overall infections						
Clinically relevant, No.	278	1964	90	725	463	3520
Rate per 1000 transplant-days (95% CI)						
0–1 mo	19.3 (15.7–23.8)	8.3 (7.5–9.2)	15.3 (10.9–21.4)	16.4 (14.3–18.8)	17.3 (14.4–20.7)	12.0 (11.1–12.8)
>1–6 mo	3.9 (3.0–5.0)	3.9 (3.5–4.3)	3.5 (2.2–5.7)	3.3 (2.7–3.9)	4.6 (3.8–5.6)	3.9 (3.6–4.2)
>6–12 mo	1.5 (1.1–2.2)	2.1 (1.9–2.4)	1.4 (.8–2.3)	1.7 (1.3–2.2)	2.6 (2.1–3.2)	2.0 (1.8–2.2)
Rate per person-years (95% CI)	1.5 (1.3–1.7)	1.2 (1.2–1.3)	1.3 (1.0–1.5)	1.3 (1.2–1.4)	1.7 (1.6–1.9)	1.3 (1.3–1.4)
Bacterial infections	152 (55)	1299 (66)	59 (66)	425 (59)	267 (58)	2202 (63)
Viral infections	89 (32)	551 (28)	21 (23)	240 (33)	138 (30)	1039 (30)
Fungal infections	36 (13)	104 (5)	10 (11)	56 (8)	57 (12)	263 (8)
Parasitic infections	1 (.4)	10 (.6)	0	4 (.6)	1 (.3)	16 (.5)
<b>Antimicrobial prophylaxis</b>						
Antipneumocystis						
TMP-SMX	184 (86)	1495 (93)	67 (92)	383 (66)	274 (96)	2403 (87)
Atovaquone	4 (2)	37 (2)	3 (4)	7 (1)	22 (8)	73 (3)
Pentamidine <sup>a</sup>	2 (1)	29 (2)	0	7 (1)	1 (0.4)	39 (1)
Antibacterial						
$\beta$ -lactam	14 (7)	258 (16)	12 (16)	129 (22)	75 (26)	488 (18)
Macrolides	0	5 (0.3)	0	1 (0.2)	36 (13)	42 (2)
Quinolones	5 (2)	252 (16)	1 (1)	38 (7)	46 (16)	342 (12)
Tobramycin <sup>a</sup>	0	0	0	0	29 (10)	29 (1)
Antiviral						
Acyclovir/valacyclovir	15 (7)	82 (5)	2 (3)	24 (4)	120 (42)	243 (9)
Gancyclovir/valgancyclovir	109 (51)	847 (53)	49 (67)	172 (30)	225 (79)	1402 (51)
Lamivudine	4 (2)	27 (2)	0	14 (2)	6 (2)	51 (2)
Antifungal						
Fluconazole	1 (1)	11 (0.7)	7 (10)	20 (4)	4 (1)	43 (2)
Mold-active azoles <sup>b</sup>	0	11 (1)	0	11 (2)	195 (68)	217 (8)
Echinocandins <sup>c</sup>	1 (1)	2 (0.1)	0	22 (4)	17 (6)	42 (2)
Amphotericin B <sup>a</sup>	8 (4)	31 (2)	1 (1)	19 (3)	234 (82)	293 (11)

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; IQR, interquartile range; TMP-SMX, trimethoprim-sulfamethoxazole.

<sup>a</sup>By aerosol.

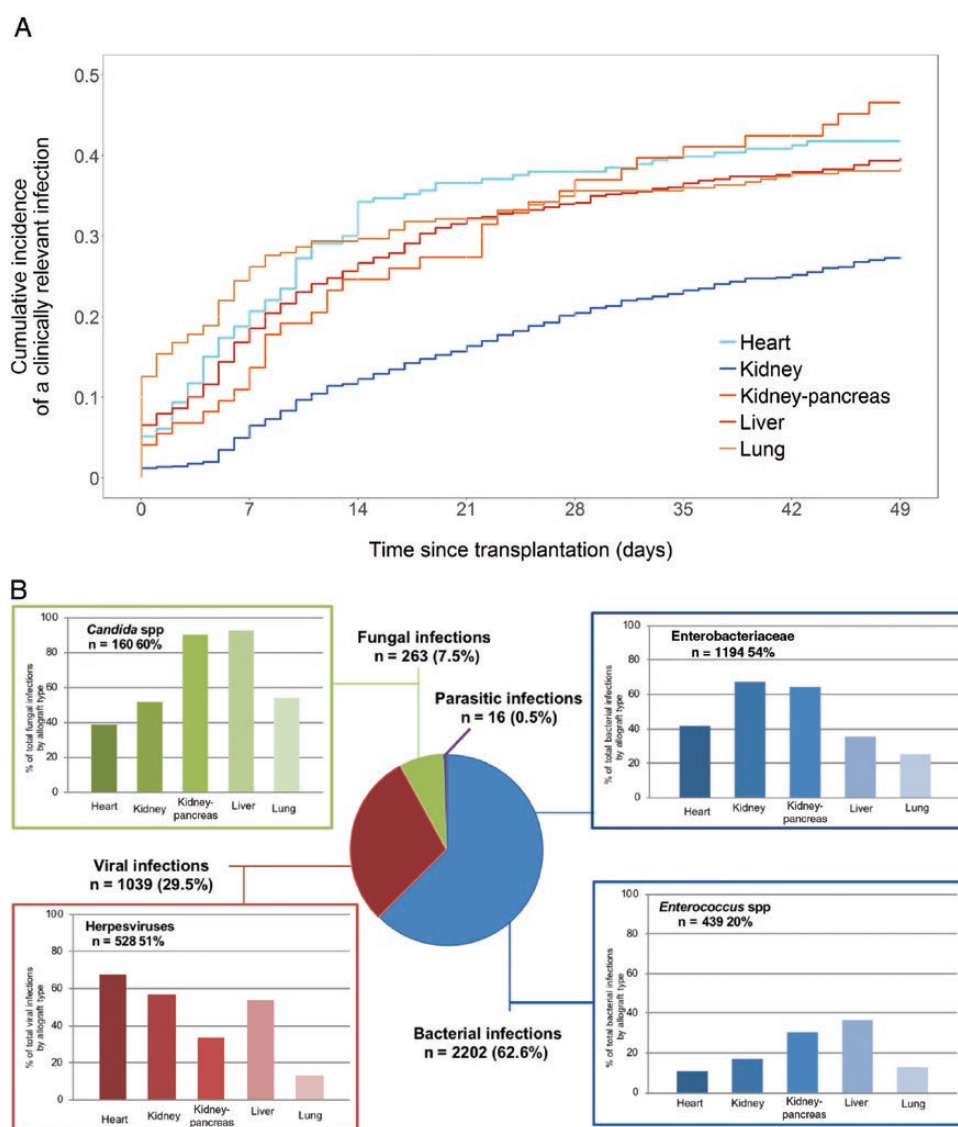
<sup>b</sup>Mold-active azoles: itraconazole, voriconazole, and posaconazole.

<sup>c</sup>Echinocandins: caspofungin and anidulafungin.

[HR], 1.83 [95% CI, 1.44–2.31];  $P < .001$ ), liver (HR, 1.66 [95% CI, 1.42–1.95];  $P < .001$ ), and lung (HR, 1.68 [95% CI, 1.35–2.09];  $P < .001$ ) transplants (Figure 1A). At 12 months posttransplantation, the cumulative incidence reached 53% for kidney, 55% for liver, 60% for heart and kidney-pancreas, and 62% for lung transplant recipients. Given the small number of parasitic infections (16), these were not included in further subanalyses. For 161 (6%) patients, the follow-up terminated before 12 months because of death, and only 6 patients were lost to follow-up. Infections were recorded as direct cause of death in 52 (2%) patients (Table 1).

#### Types and Duration of Prophylaxis

In the first year posttransplantation, prophylaxis was given to 2617 (95%) SOT recipients. Anti-*Pneumocystis* prophylaxis included trimethoprim-sulfamethoxazole, prescribed to 87% of patients (2403/2761) for a median duration of 179 days (interquartile range [IQR], 119–281 days; Table 1; Supplementary Figure 2). Antibacterial prophylaxis provided to 27% of patients (754/2761) included  $\beta$ -lactam antibiotics (488 patients; median duration, 8 days [IQR, 2–32 days]) and quinolones (342 patients; median duration, 12 days [IQR, 7–35 days]). Antiviral prophylaxis provided to 57% of patients (1569/2761; median



**Figure 1.** Incidence and distribution of clinically relevant infections by allograft type in 2761 solid organ transplant (SOT) recipients. A, Cumulative incidence censored for competing events (proven infection, graft loss, death, second transplantation) of first clinically relevant infections by allograft type until week 7 after SOT. B, Relative percentage of clinically relevant infections with predominant pathogens by allograft type.



duration, 95 days [IQR, 59–180 days]) included 98% of lung transplant recipients. Ganciclovir/valganciclovir was given to 51% (1402/2761) patients. Antifungal prophylaxis was infrequently prescribed (18% [487/2761] of all SOT recipients) and was mostly administered to lung transplant recipients (median duration, 358 days [IQR, 34–362 days]).

### Burden of Clinically Relevant Infections

Bacterial infections predominated, causing 63% (2202/3520) of all infections (Table 1; Figure 1B). Thirty-nine percent (1086/2761) of patients developed at least 1 proven bacterial infection. Hepatic and other intra-abdominal infections (158/450 [35%]) predominated in liver recipients, whereas the urinary (938/1355 [69%]) and respiratory tracts (143/273 [52%]) were most frequently involved in kidney and lung transplant recipients, respectively (Figure 2A). Bacteremia was documented in 18% (405/2202), with 22% (89/405) occurring between 6 and 12 months after transplantation (Supplementary Table 2). Enterobacteriaceae were identified in 54% (1194/2202) of infections (Figure 1B; Supplementary Table 1; Supplementary Figures 4 and 5), with *Escherichia coli* and *Klebsiella* spp predominating (1033/2202 [47%]). Fifteen percent (65/449) of tested *E. coli* and *Klebsiella* spp produced extended-spectrum  $\beta$ -lactamases (ESBL), whereas no carbapenemase-producing bacteria were detected. *Enterococcus* spp and *Pseudomonas aeruginosa* were responsible for 20% (439/2202) and 9% (200/2202) of infections, respectively. Twenty-three percent (17/74) of tested *P. aeruginosa* isolates were multidrug resistant. *Staphylococcus aureus* (79/2202 [4%]) and *Clostridioides difficile* (111/2202 [5%]) were infrequent pathogens. Opportunistic bacteria, such as *Legionella* spp, *Nocardia* spp, and *Mycobacteria* spp, were responsible for 0.6% (14/2202) of infections.

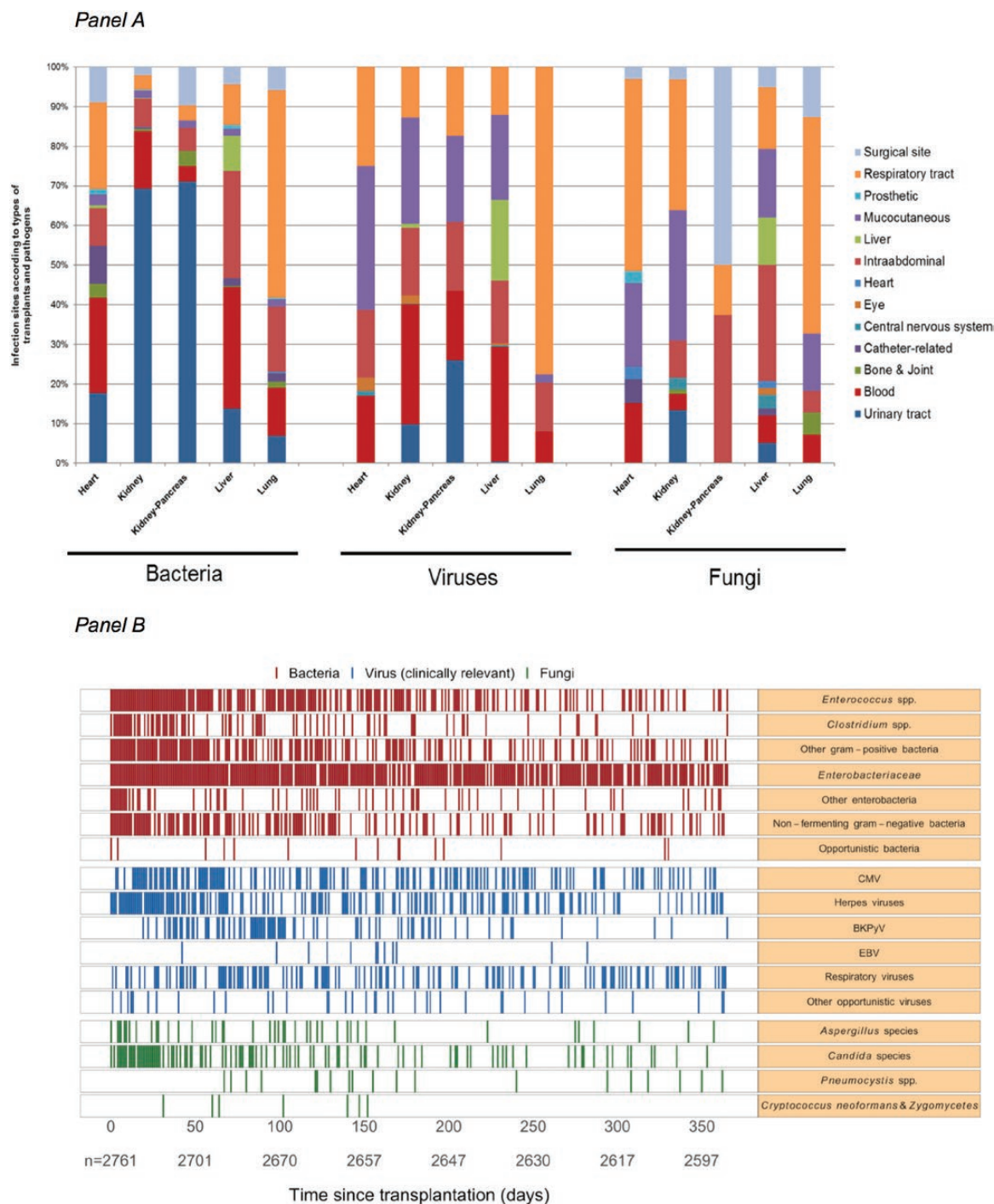
Thirty percent of all infections (1039/3520) were viral, including 77 viral syndromes, 314 probable viral infections, and 648 proven viral infections (Table 1; Figure 1B). Except for lung transplant recipients, in whom respiratory tract infections predominated (107/133 [80%]), sites of viral infections were similar across different transplantations and consisted of mucocutaneous (239/1039 [23%]), respiratory tract (233/1039 [22%]), and intra-abdominal/hepatic (228/1039 [22%]) infections (Figure 2A; Supplementary Figures 6 and 7). Herpesviruses predominated (528/1039 [51%]). Cytomegalovirus (CMV) presented as viral syndrome ( $n = 69$ ), probable infection ( $n = 57$ ), and proven ( $n = 76$ ) infection, altogether 5.7% (202/3520) of all clinically relevant infections, BK polyomavirus viremia was seen in 275 (275/1685 [16%]) and diagnosed as probable ( $n = 39$ ) and proven nephropathy ( $n = 60$ ) in 6% (99/1685) of kidney and kidney-pancreas transplant recipients, constituting 17% (99/572) of viral infections in these patients.

Fungus caused 170 proven and 93 probable infections, representing 8% (263/3520) of all clinically relevant infections (Table 1; Figure 1B). The respiratory tract was affected in 34% (88/263) and predominated in lung transplant recipients, whereas intra-abdominal/hepatic infections predominated in kidney-pancreas and liver transplant recipients (Figure 2A). Fungemia and central nervous system involvement were documented in 3% (17/263) and 2% (6/263), respectively. *Candida* spp predominated (160/263 [60%]) and prevailed in liver transplant recipients (52/56 [93%]) (Supplementary Figures 8 and 9). Nineteen percent (50/263) of infections were due to *Aspergillus fumigatus*, affecting lung (20/50 [40%]) and kidney transplant recipients (14/50 [28%]), whereas *Pneumocystis jirovecii* infections (20/263 [8%]) occurred mainly in kidney transplant recipients (15/20 [75%]) clustered in a single center that did not provide prophylaxis between 2008 and 2012 [12].

### Timeline of Clinically Relevant Infections

Bacterial infections predominated during the entire year (Supplementary Figure 10). Infections due to Enterobacteriaceae occurred at high frequency throughout the observation period, whereas infections due to *Enterococcus* spp and nonfermenting gram-negative bacteria occurred at high rates during the first 180 and 150 days, respectively, and continued thereafter at reduced but still regular pace (Figure 2B). CMV and herpes simplex virus (HSV) infections peaked at 50 days and continued during the entire observation period. Respiratory virus infections (influenza, parainfluenza, respiratory syncytial virus, human metapneumovirus, and rhinovirus) occurred throughout the first year posttransplantation. *Aspergillus* infections occurred primarily in the first 150 days, and *Pneumocystis* as isolated events between 50 and 350 days.

The timelines of clinically relevant infections differed between types of transplantations (Figures 3 and 4). Enterobacteriaceae, predominating during the entire year as urinary pathogens in heart, lung, and kidney transplant recipients, and as digestive tract pathogens in liver transplant recipients, were a major cause of bloodstream infections in kidney and liver transplant recipients. Respiratory tract infections due to *P. aeruginosa* and Enterobacteriaceae were restricted to the first month in heart transplant recipients and occurred throughout the first year in lung and kidney transplant recipients. *Enterococcus* spp were frequent during the entire year as urinary tract pathogens in kidney and as tract pathogens in liver transplant recipients, and were frequently associated with bloodstream infections in liver transplant recipients. *Candida albicans* bloodstream infections were observed during the first month in liver and heart transplant recipients and were associated with digestive tract infections in liver transplant recipients. CMV and HSV infections occurred with similar timelines in kidney, liver, and heart transplant recipients.



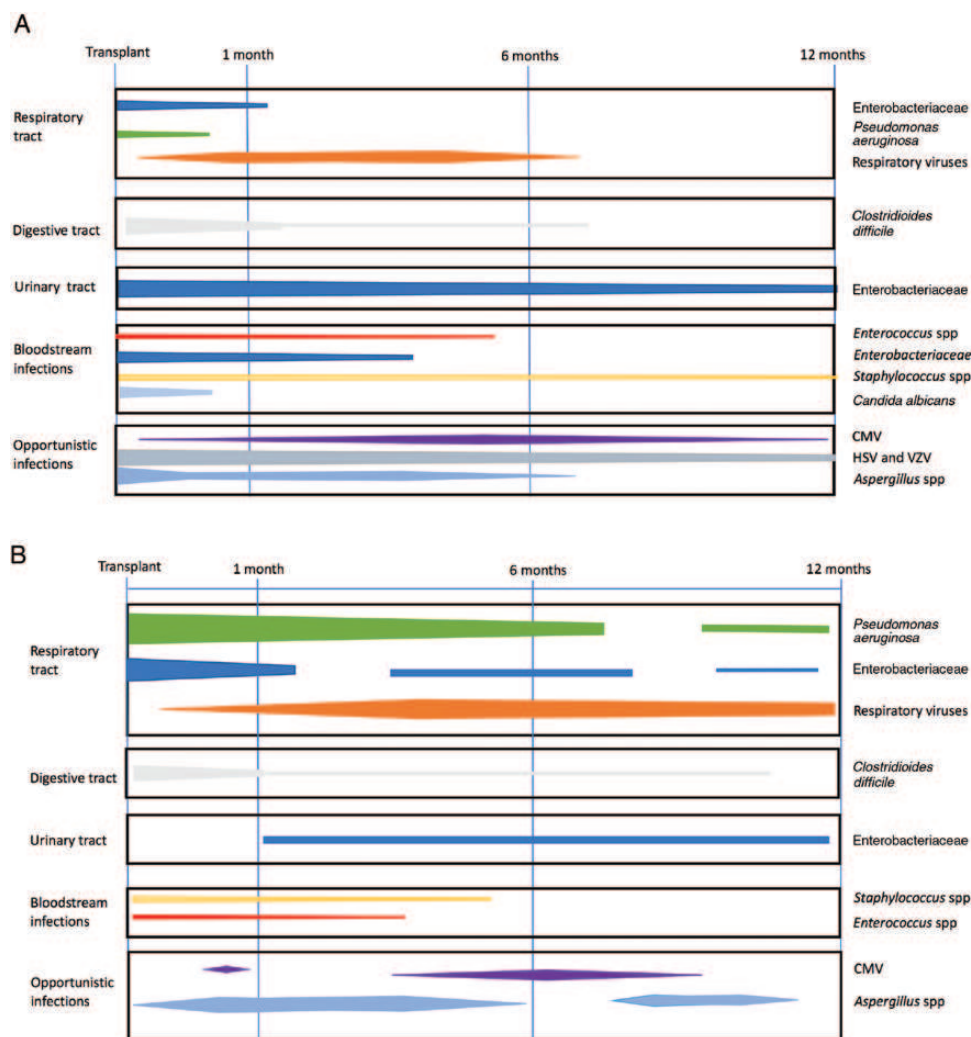
**Figure 2.** Distribution by infection site and timeline of infections. A, Distribution (%) of 2202 clinically relevant bacterial, 263 fungal, and 1039 viral infections by infection site and allograft type. Percentages are normalized for each allograft type and represent the relative involvement of each site. B, Temporal distribution of clinically relevant infections by pathogen. Each bar represents an individual event: bacterial (red), viral (blue), and fungal (green) infection. The number of patients under observation is indicated at specific time points. Other gram-positive bacteria: coagulase-negative staphylococci, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus* spp. Enterobacteriaceae: *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp. Nonfermenting gram-negative bacteria: *Pseudomonas aeruginosa*, *Burkholderia* spp, *Acinetobacter* spp, *Stenotrophomonas maltophilia*. Opportunistic bacteria: *Nocardia* spp, *Legionella* spp, *Mycobacteria* spp other than tuberculosis. Herpesviruses include herpes simplex virus, varicella zoster virus, and human herpesviruses 6 and 8. Abbreviations: BKPyV, BK polyomavirus; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

## DISCUSSION

In 1998, Fishman and Rubin, the clinical pioneers of TID, distinguished 3 periods of infections following SOT: (1)

nosocomial infections until 1 month posttransplantation; (2) opportunistic infections from 1 month to 6 months; and (3) community-acquired or persistent infections after 6 months



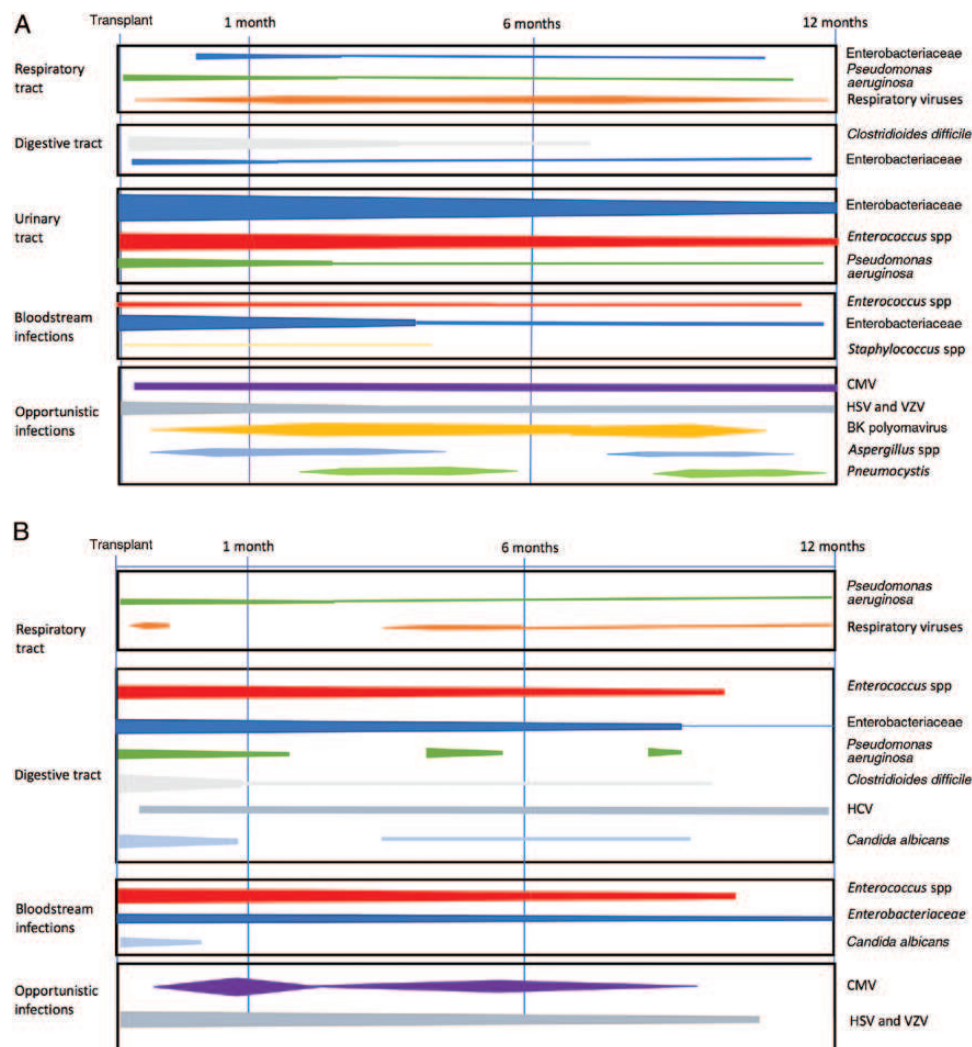


**Figure 3.** Timelines of the most significant clinically relevant infections for heart (A) and lung (B) transplant recipients according to predominant infection sites. The timeline and relative burden are based on the temporal distribution of 278 infections in 213 heart transplant recipients and 463 infections in 286 lung transplant recipients. Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella zoster virus.

[1]. This important timeline has successfully guided the administration of antimicrobial prophylaxis and the development of diagnosis-based preemptive strategies, as well as life-saving empiric therapies [3]. In this STCS covering comprehensively all clinically relevant infections over the first 12 months after SOT in >2700 patients, we found that (1) infections were frequent, occurring at high incidence even 6 months after transplant; (2) timelines of infections had organ specificities; (3) traditional opportunistic pathogens were rare and occurred throughout the 12 months; and (4) bacteria predominated being responsible for >60% of all infections throughout the year. Thus, despite an increased potency of immunosuppression in the current era, the impact of opportunistic infections could be at least partially counteracted through targeted prophylaxis, surveillance, and risk stratification spearheaded by Rubin and Fishman. Previous registries and clinical trials, focused on specific transplant

populations, pathogens, or particular infection sites, provided limited data to determine the overall impact of these measures on the global burden of infections [7, 13–17]. Reports from the Spanish Network for Research on Infection in Transplantation (RESITRA) cohort suggested a decline in incidence of inpatient infections from 8.3 episodes per 1000-transplant-days during the first month to 0.4 episodes per 1000 transplant-days between 6 and 12 months after SOT [4, 5]. However, relevant infections occurring at distant hospitals, or as outpatients, were not captured.

The extensive medical network in Switzerland allows a very close medical follow-up, with all infections occurring during hospitalization or as outpatients being taken care of and documented in the transplant center. Furthermore, particular care was taken in the STCS to assure optimal data quality, based on standardized definitions and quality audits. Consequently,



**Figure 4.** Timelines of the most significant clinically relevant infections for kidney (A) and liver (B) transplant recipients according to predominant infection sites. The timeline and relative burden are based on the temporal distribution of 1964 infections in 1612 kidney and 725 infections in 577 liver transplant recipients. Abbreviations: BKPyV, BK polyomavirus; CMV, cytomegalovirus; HCV, hepatitis C virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

our data guarantee a comprehensive view of all clinically relevant infections during the first year following transplantation. Unlike previous reports, the overall burden of infection in this cohort remained elevated during the entire year. Twenty-four percent of patients at risk between 6 and 12 months post-SOT developed 28% of all infections, with an incidence of 2 infections per 1000 transplant-days. Forty-seven percent of these late infections required hospitalization, underlying their severity. As previously suggested by others, our study demonstrates the efficacy of present antimicrobial prophylaxis against opportunistic pathogens [4, 18]. Indeed, we observed a low number of opportunistic infections in all types of SOT recipients frequently occurring at later timepoints following transplantation, once prophylaxis is discontinued. Better defining populations at risk for these opportunistic infections will be crucial to further improve the present prophylactic strategies, mostly designed for early infections [12, 19–26]. *Aspergillus fumigatus*, responsible

for 1.4% of all infections, is a serious concern, particularly in liver transplant recipients, because of the associated high mortality [26]. The scarcity of CMV disease, presenting a bimodal distribution, reflects the success and shortcomings of prophylactic and preemptive strategies used in Switzerland [27]. This calls for additional efforts to better define timing to discontinue prophylaxis, potentially by testing specific cell-mediated immunity against CMV [28]. HSV and varicella zoster virus are the most frequently encountered viral infections; with HSV-seropositive heart and liver transplant recipients not receiving CMV prophylaxis being at highest risk. Their burden should be balanced with the level of morbidity, drug toxicity, and costs of widened prophylaxis in new recommendations [29]. BK polyomavirus nephropathy, diagnosed in 3.6% of kidney and kidney-pancreas recipients, has emerged as a concern because of its serious consequences in kidney-transplant recipients [30–32].

Our study further highlights the preponderance of bacterial pathogens. Infections due to Enterobacteriaceae (*E. coli*, *Klebsiella* spp), *P. aeruginosa*, and *Enterococcus* spp, previously described as being limited to the first month predominated, throughout the entire year. Together these microorganisms were responsible for 48% of all infections. In contrast to previous reports, suggesting that bloodstream infections rarely occur after 180 days post-SOT, we found a persisting high frequency of bacteremia with 22% of all episodes occurring after 6 months [7]. Preventing these infections will be a major challenge. Indeed, many of these infections involve the surgical site and the allograft itself, and are favored by surgical complications including anastomotic leaks and strictures, undrained collections, and indwelling catheters [3, 33, 34]. Major efforts to reduce these risk factors, including improved surgical techniques, adequate source control, and early removal of indwelling catheters and prosthetic material will be essential. Infections with ESBL- and carbapenemase-producing *E. coli* and *K. pneumoniae*, multidrug-resistant and pan-drug-resistant *P. aeruginosa*, and vancomycin-resistant enterococci are on the rise worldwide and affect SOT recipients, with an important impact on survival [15, 35–40]. The major burden represented by these particular bacterial species in SOT recipients in our study is particularly alarming. Switzerland currently has a rather low incidence of bacterial resistance compared with other countries. The rates of multidrug-resistant bacterial infection in our cohort should therefore serve as a caution to transplant programs in other countries where resistance rates may be even higher [41, 42]. Furthermore, clinicians initiating empiric therapies need to be aware about pathogen and infection timelines differences according to type of transplant.

We wish to acknowledge potential limitations. Though we used concise definitions and unified identification procedures, some infections might have been miscoded, thereby overestimating some infections. Due to the inclusion of microbiologically documented infections, difficult-to-authenticate infections (ie, respiratory tract infections) might have been underrepresented. Despite efforts to identify all inpatient and outpatient events, we cannot exclude that some infections were not captured and hence underestimated. Kidney transplant recipients represented 61% of our population, potentially influencing the rates of disease manifestations. However, capturing infections in a large number of non-kidney transplant recipients during the same era revealed similar trends among different pathogen types and infection rates, strengthening the robustness of our observations. Our study was not designed to determine the risk of infections in the presence or absence of antimicrobial prophylaxis, or potential associations between infections. Finally, the results of our study may not be applicable to programs in other geographic settings, having different microbial epidemiology and prophylaxis strategies.

## CONCLUSIONS

Certain aspects of the 1998 TID timeline remain true in the current era of potent immunosuppression, screening, and prophylaxis. Translating the TID timeline into prophylactic strategies, the incidence of opportunistic infections has been reduced and partly shifted to later timepoints. The first month remains characterized by the highest burden of infections, with healthcare-associated infections prevailing. However, bacterial infections, mainly affecting the allograft and transplant site, continue at high rates throughout the entire year, urging for better control. The transplant-specific timelines presented here should help clinicians to target patient-adapted prophylactic and empiric treatments. The high burden of Enterobacteriaceae, *Pseudomonas*, and *Enterococcus* with rising antimicrobial resistance is worrisome and urges for the development of new approaches and antimicrobials to guarantee improved graft and patient survival.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

**Author contributions.** C. v. D., N. M., S. S., H. H., O. M., and P. M. participated in the study design, analysis of data, and writing of the manuscript. S. S., R. S., and M. K. participated in the statistical analysis. A. C., C. H., N. K., M. W., C. G., K. B., C. B., and D. N. participated in data collection. All authors participated in critically reviewing the manuscript and have given final approval of the version to be published.

**Acknowledgments.** The authors thank all patients who participate in the Swiss Transplant Cohort Study (SCTS), the study nurses, the central and local data managers, and all of the investigators involved in the STCS (see Appendix); Angela Huttner and Dionysios Neofytos for critical review and editing of the manuscript; and Sanda Branca for statistical support. All data included in the present study belong to the STCS. The dataset used for this study is stored at the STCS data center and is available upon request.

**Financial support.** This work was funded as a nested project in the framework of the Swiss Transplant Cohort Study (STCS) supported by the Swiss National Science Foundation (grant numbers 3347CO-108795, 33CS30-148512, and 33CS30-177522) and the Swiss University Hospitals (G15) and transplant centers.

**Potential conflicts of interest.** O. M. reports grants from Lophius Biosciences, outside the present work. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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## APPENDIX

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